Cellular Automata Computational Model of Microvascular Remodeling

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We have developed an innovative computational cellular automata (CA) model to predict network patterning aspects of microvascular remodeling that result from discrete cellular behaviors, cell-cell interactions, and cell-extracellular matrix signaling. Microvascular remodeling in the adult animal is critical to physiological growth and adaptation to exercise, and plays an important role in pathological events such as tumorigenesis, wound healing, and ischemic disorders of the heart and limbs. Stimuli, such as alterations in hemodynamic stresses and localized hypoxia, invoke angiogenesis, or capillary sprouting, and arteriogenesis, or the formation of arterioles. Many cellular behaviors, such as proliferation, differentiation, migration, and apoptosis contribute to these processes, and coordination of microvascular network remodeling events is achieved via combinations of biochemical and biomechanical signals. This study examines patterning changes in subcutaneous microvascular networks induced by two stimuli: 1) localized changes in hemodynamic stress, and 2) focal applications of exogenous vascular endothelial growth factor (VEGF) and models the spatial and temporal growth response using a novel cellular automata (CA) computer simulation. Over 50 rules obtained from published experimental data govern the independent behaviors of thousands of interacting cells and the diffusible growth factor profiles of their tissue environment. From initial network patterns obtained directly from experimentally-imaged *in vivo* networks, the model predicts emergent patterning responses to the two epigenetic stimuli. The CA model predicts experimentally-verified changes in spatial vascularity and vessel maturation, or perivascular cell recruitment, in response to the growth factor stimuli. We suggest that this CA approach to studying a complex biological patterning process has the potential to broadly impact biomedical discovery because it is 1) applicable to any biological system composed of discrete but interacting cells, 2) capable of integrating vast amounts of quantitative experimental data in a useful way to generate functional knowledge, suggest testable hypotheses, and verify experimental data, and 3) useful for the prediction of unified and consistent cellular mechanisms underlying vascular growth and adaptation.

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